

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

## A Rational Approach to the Development of Drug Combinations in Thoracic Oncology



D. Ross Camidge, MD, PhD  
 Director of Thoracic Oncology  
 Professor, Division of Medical Oncology  
 Joyce Zeff Chair in Lung Cancer Research  
 University of Colorado Anschutz Medical Campus  
 Denver, Colorado

**H&O** What is the typical approach to the development of drug combinations in oncology?

**DRC** In clinical trials, drug combinations can reflect several scenarios. A trial can evaluate an established licensed drug in combination with an unapproved agent. There may be 2 novel, unlicensed drugs. In a more complex scenario, a new combination regimen may be used to treat the same cancer existing in 2 different body compartments, for example, the brain and another area. This type of trial will evaluate whether an additional treatment can increase the activity within the brain.

In a trial of an established drug plus an unapproved drug, the traditional approach is to evaluate the established drug given at the standard dose plus the novel

The use of biomarkers can help select appropriate patients for trials of combination therapies.

agent given at the highest dose shown to be safe. When evaluating a combination of novel drugs, a trial might start each drug at slightly below the expected monotherapy dose, and increase the doses of each separately in each new dose-escalation cohort.

In thoracic oncology, trials of combination therapies have led to new approvals from the US Food and Drug Administration (FDA) most often when a novel agent is added to standard chemotherapy. For example, bevacizumab (Avastin, Genentech) is approved in combination with first-line platinum/paclitaxel chemotherapy, and ramucirumab (Cyramza, Lilly) is approved for use with docetaxel as second-line chemotherapy. The FDA has approved one combination of novel agents for patients with lung cancer: dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis) for V600E-mutant non-small cell lung cancer. (This regimen is also used in *BRAF*-mutant melanoma.) Several other combinations are being considered, particularly in the field of acquired resistance to targeted therapy and primary resistance to immunotherapy.

**H&O** How are combination regimens typically identified for evaluation in clinical trials?

**DRC** In some cases, drugs are tested in combination merely because they are produced by the same pharmaceutical company—keeping things within one portfolio of drugs. A more rational approach would be based on promising preclinical and/or clinical data.

**H&O** What are some recent discoveries about thoracic cancers that can help foster a rational approach?

**DRC** The use of biomarkers can help select appropriate patients for trials of combination therapies. As an

example, researchers have begun to recognize mechanisms of acquired resistance that emerge during treatment with certain tyrosine kinase inhibitors (TKIs). The challenge is to identify subgroups of patients with particular mechanisms that would increase their likelihood of benefiting from the addition of another agent to standard treatment with the original TKI. Moving forward, it will be key to identify these patients and develop a predictive biomarker. Assessing the frequency of particular biomarkers can also help inform the size of clinical trials, either in terms of the number of people who would need to be screened for the presence of a marker, or to estimate the chances of success with an unenriched approach in a given population.

### H&O What technologies can be used to identify possible drug combinations?

**DRC** Preclinically, it is possible to test agents via cell lines, but this approach is simplistic. Evaluation of immunology combinations requires immunocompetent mouse models. It will be necessary to develop predictive biomarkers to identify patients with mutations in certain pathways that render them candidates for combination therapy.

### H&O Have any successful drug combinations in lung cancer been developed based on a rational approach?

**DRC** This area is still a work in progress. In non-small cell lung cancer, patients with amplification of mesenchymal-epithelial transition factor (*MET*) as a mechanism of acquired resistance to the epidermal growth factor receptor (*EGFR*) TKIs and an *EGFR* mutation can be treated by adding a *MET* inhibitor to the *EGFR* TKI. The problem is that *MET* amplification can be quantified in different ways, and it is a continuous variable. The precise level of *MET* expression that drives the cell and would signal benefit from combination treatment remains under investigation.

There are competing philosophies in terms of the best approach to the use of biomarkers in clinical trials of combination regimens in this setting. The most inclusive biomarker approaches maximize the number of patients who might benefit from the treatment, but may minimize the average benefit. A drug company might prefer this approach to also maximize the market size if the study generates positive results. In contrast, a stricter biomarker approach may identify a smaller subpopulation of patients, challenging adequate enrollment. However, it may lead to high rates of response among these highly selected patients. Then it might be possible later, after a positive study in the “surest bet” population, to identify

other groups of patients who might also benefit, albeit to a lesser extent. The former approach has been relatively unsuccessful. The second strategy has a higher chance of success and, in my opinion, is the better initial approach.

### H&O Are there examples of drug combinations with effects that were not anticipated based on single-agent data or preclinical models?

**DRC** Evaluations of the combination of programmed death 1 (PD-1) or PD ligand 1 agents with TKIs against anaplastic lymphoma kinase (ALK) in patients with *ALK* gene–rearranged lung cancer were often driven by the fact that the same company made both drugs. These single-arm studies were almost impossible to interpret in terms of efficacy because the TKIs have very high response rates as monotherapy. However, the combination regimens were much more toxic than expected. The major toxicities consisted of liver inflammation and lung inflammation. They could not have been predicted from a petri dish, which provides only an isolated model.

In general, as was seen with these studies of a TKI plus immunotherapy, it is almost impossible to accurately interpret efficacy results from a single-arm study in which the backbone of the combination is known to have significant activity by itself. If there is an 80% response rate with one drug, it is hard to show that the other drug is adding very much. Another example is provided by many initial immunotherapy combination trials. Treatment with pembrolizumab (Keytruda, Merck) or nivolumab (Opdivo, Bristol-Myers Squibb) can be associated with response rates of 20% or 80%, depending on the patient population. If a single-arm study of such an agent in combination with a novel agent in an immunotherapy-naïve population shows a response rate of 30%, it could be (and often has been) misinterpreted as an improvement compared with historical control data showing the lower range of response—20%. However, the response rate could be as high as 80%, with no benefit from the second drug, depending on the characteristics of the enrolled patients.

### H&O Are there any barriers to the research of combination regimens in oncology?

**DRC** In some cases, there is very little money for clinical research other than from the pharmaceutical industry, and the biggest barrier there is that it may not be possible to test combinations of agents that are produced by different companies. Not everyone plays nicely together, or wants to divide the costs equally. There are some governmental solutions, with a range of drugs from different companies covered by a National Cancer Institute agreement. However, you still come back to who is paying for the actual

running of the trial. That remains, perhaps, the biggest challenge for all clinical research these days.

### Disclosure

*Dr Camidge has received honoraria and/or research funding from Takeda, CBT Pharmaceuticals, Daiichi Sankyo, G1 Therapeutics, Biothera, Blueprint Medicines, AstraZeneca, Arrys/Kyn, Regeneron, Hengrui, Ribon, BMS, Roche/Genentech, Inivata, Genoptix, Mersana Therapeutics, Ignyta, Lycera, and Revolution Medicines. As a local principal investigator, Dr Camidge has received institutional funding for conducting clinical trials from AbbVie, AstraZeneca, BMS, Hansoh, Lycera, MedImmune, Merck, Pfizer, Phosphatin, Roche/Genentech, Seattle Genetics, Symphogen, and Takeda.*

### Suggested Readings

Byers LA, Horn L, Ghandi J, et al. A phase 2, open-label, multi-center study of amuvatinib in combination with platinum etoposide chemotherapy in platinum-refractory small cell lung cancer patients. *Oncotarget*. 2017;8(46):81441-81454.

Camidge DR, Berge EM, Doebele RC, et al. A phase II, open-label study of ramucirumab in combination with paclitaxel and carboplatin as first-line therapy in patients with stage IIIB/IV non-small-cell lung cancer. *J Thorac Oncol*. 2014;9(10):1532-1539.

Camidge DR, Blais N, Jonker DJ, et al. Sunitinib combined with pemetrexed and cisplatin: results of a phase I dose-escalation and pharmacokinetic study in patients with advanced solid malignancies, with an expanded cohort in non-small cell lung cancer and mesothelioma. *Cancer Chemother Pharmacol*. 2013;71(2):307-319.

Liu SV, Camidge DR, Gettinger SN, et al. Long-term survival follow-up of atezolizumab in combination with platinum-based doublet chemotherapy in patients with advanced non-small-cell lung cancer. *Eur J Cancer*. 2018;101:114-122.

Paller CJ, Bradbury PA, Ivy SP, et al. Design of phase I combination trials: recommendations of the Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee. *Clin Cancer Res*. 2014;20(16):4210-4217.

von Pawel J, Harvey JH, Spigel DR, et al. Phase II trial of mapatumumab, a fully human agonist monoclonal antibody to tumor necrosis factor-related apoptosis-inducing ligand receptor 1 (TRAIL-R1), in combination with paclitaxel and carboplatin in patients with advanced non-small-cell lung cancer. *Clin Lung Cancer*. 2014;15(3):188-196.e2.

York ER, Varela-Garcia M, Bang TJ, Aisner DL, Camidge DR. Tolerable and effective combination of full-dose crizotinib and osimertinib targeting *MET* amplification sequentially emerging after T790M positivity in *EGFR*-mutant non-small cell lung cancer. *J Thorac Oncol*. 2017;12(7):e85-e88.

### Erratum

Because of an editing error in the June 2019 issue, the interview with Neil A. Goldenberg, MD, PhD, called “Venous Thromboembolism in Children,” incorrectly referred to CHAT as the “Children’s Hospital Association Thrombosis project” instead of the “Children’s Hospital-Acquired Thrombosis project.” We have made the correction to page 327 of the online version at [www.hematologyandoncology.net](http://www.hematologyandoncology.net).